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During the period of the study we researched the effects of 25 Hz rTMS in 12 patients with PD. Eight rTMS sessions were performed over a four-week period. Four cortical targets were stimulated in each of the sessions (left and right motor and dorsolateral prefrontal cortex) with 300 pulses each. We haven't done any type of the interim statistical analysis of the results at this point and will not do so until enough data has been collected. Preliminary results indicate the cumulative reduction of bradykinesia in the course of rTMS sessions. This manifested itself by a decrease of the time needed to execute motor tests. rTMS used under the parameters of the regimen is safe in patients with PD.

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Introduction

The drug treatment of akinesia and rigidity in Parkinson's disease (PD) currently revolves around dopamine containing medications. PD is typically easy to treat early in the disease, but later the response declines and complications develop. Postural instability associated with gait disorder is usually a very disabling and a less treatable manifestation of PD, and it represents a major contributing factor in progression from mild bilateral disease to wheelchair confinement (Paulson, Stern, 1997).

TMS is a tool that allows non-invasive stimulation of the cerebral cortex. Many researchers have used TMS to understand PD pathophysiology, but only a few researchers have used it in therapeutic trials. In the initial study of drug-free patients, repetitive TMS (rTMS) applied to the primary motor areas, contralateral to the performing hand, shortened the time that drug-free PD patients took to complete the Grooved Pegboard Test (Pascual-Leone et al., 1994a). These results were not reproducible, however (Ghabra et al., 1999). Single-pulse focal TMS has shortened the simple reaction time in PD patients (Pascual-Leone et al., 1994b). In a different PD study, rTMS at 1 Hz frequency for 15 minutes increased the velocity of finger tapping (Sommer et al., 1998). Siebner et al. (1999, 2000) found that 5 Hz TMS over the motor cortex improved ballistic movements for 20 minutes and decreased contralateral arm motor scores 1 hour after the TMS session. While some of these studies are encouraging, rTMS cumulative effects were not studied, and it is unclear whether rTMS might have any long-lasting therapeutic effects (weeks or months) in persons with PD who are already receiving optimal available therapy. Intriguingly, recent studies with low frequency rTMS, with large circular coils over the vertex or dorsolateral prefrontal cortex (DLPC) in patients receiving levodopa/carbidopa, reported a relatively long-lasting therapeutic effect (Mally, Stone, 1999; Shimamoto et al., 2001). The reasons for selecting rTMS frequency and target in these studies are unclear. The synergistic effect of rTMS and L-DOPA might be assumed, however, based on this data. Prefrontal TMS with a circular coil increases dopamine release in the caudate nucleus of healthy humans (Strafella et al., 2002). Recently, the same group reported similar effects on the motor cortex (MC) TMS (personal communication). TMS also increased dopamine concentration in rat striatum and hippocampus, and decreased it in the prefrontal cortex (Belmaker and Grisaru, 1998). Long-lasting (months) improvement of Parkinsonian symptoms and increased CSF monoaminergic metabolites were also found after ECT in patients who were receiving L-DOPA medication, further supporting the synergistic assumption (Balldin et al., 1982, Fall et al., 1995). Concentration of dopamine and its metabolites in the prefrontal cortex were increased because of ECT (Yoshida et al., 1998). "Maintenance" ECT has been proposed for the treatment of PD (Aarsland et al., 1997; Fall et al., 1995, 1999).

Body

The first patient was enrolled in the study on December 11, 2002, when the FDA and US Army IRB finally approved the study protocol. Twelve (12) patients with Parkinson's disease have been recruited into the study so far. Patients' ages ranged from 52 to 81 years. The duration of the disease varied from 7 to 25 years. Six (6) subjects were randomly included in the real TMS group. In two (2) of the five (5) patients, the study has been completed. This included

Parkinsonian symptom evaluation for one month after the end of the rTMS sessions. Three (3) of the six (6) patients are still in the study. One (1) patient was excluded (see adverse effects).

Of the five (5) patients included in the placebo group, three (3) completed the study, and two (2) are still participating in the protocol; one (1) of them is still receiving placebo rTMS, and his data is not reported below. One (1) of the patients in the placebo group withdrew from the protocol after three (3) rTMS sessions (see adverse effects).

One (1) of the patients recruited for the study, after signing the consent form and undergoing initial testing according to the protocol (neurological examination, rating with UPDRS, SRTT), decided to withdraw from the study. The patient was not randomized, and no TMS sessions were performed.

Summary of anticipated and unanticipated adverse effects: The results of 43 real rTMS sessions and 37 placebo rTMS sessions can be analyzed at this stage of the study from the point of view of the safety of the magnetic stimulations in PD. One (1) of the patients in the rTMS group was excluded from the study after the first rTMS session because 100% of the motor threshold rTMS was painful to her (minor side effect, anticipated adverse effect). One (1) of the patients in the placebo group withdrew from the protocol after three (3) rTMS sessions because he considered the natural variation of his Parkinsonian symptoms to be the result of the experimental treatment (minor side effect, anticipated adverse effect). No new risks were found based on our results or from other publications.

We haven't done any type of the interim statistical analysis of the results and will not do so until enough data has been collected, formal interim analysis is not part of the protocol design. Described below are changes of the complex movements, speed and walk speed, which have to be considered as preliminary.

Bradykinesia measurement was done by assessing the time taken to walk a 10-meter distance and to execute the complex movement test. To do the walk test, patients were instructed to walk as fast as they could at this point. They performed one test walk before the first measurement was done, and one test before and after each rTMS session. Results of sessions done during "on" periods are presented. rTMS sessions were done over a four-week period.

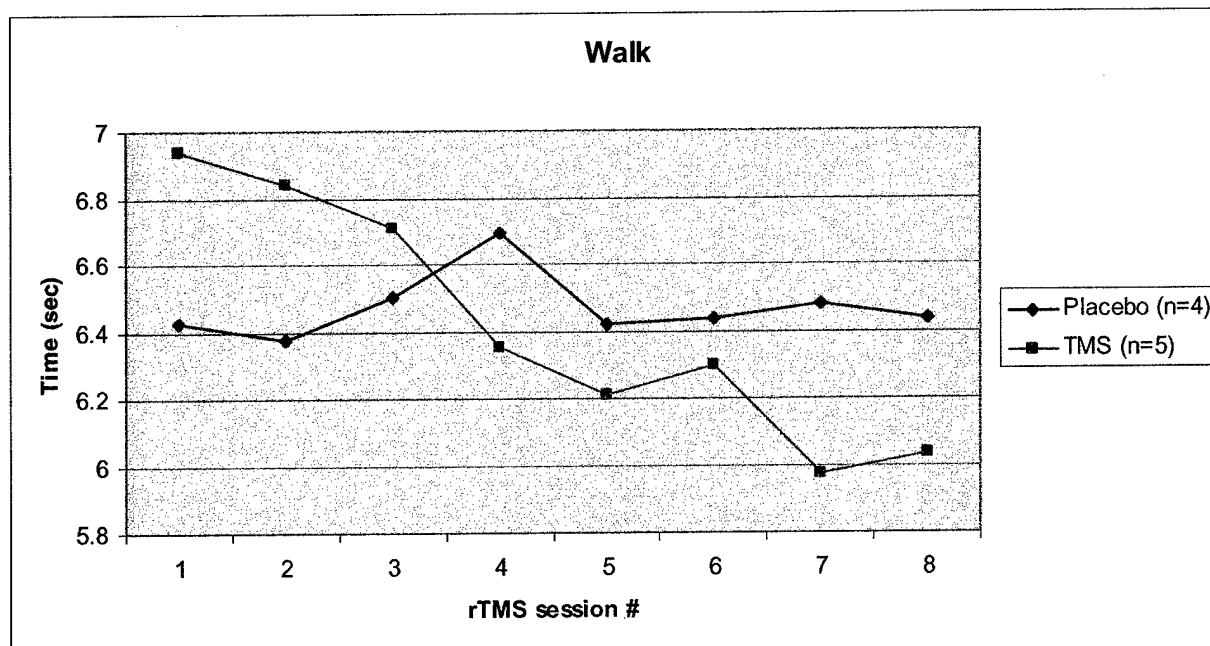


Fig.1. Time of the 10-meter distance walk (averaged data).

Abscissa – number of the rTMS sessions done in each of the patients. Ordinate – time to walk the 10-meter distance. The measurements before and after each rTMS session are combined. Each point represents two (2) measurements.

Gradual cumulative decrease of the time was observed in patients undergoing the real rTMS, though no obvious slope could be seen in the placebo group over the same time and number of TMS sessions.

Complex movement test was done before and after each of the rTMS sessions. Combined movement testing was performed on left and right hands. Testing measured time of execution and included ten (10) movements combining flexion and extension in the elbow joint with clenching and unclenching of the wrist. Patients were instructed to do that as fast as they could and to do it keeping the same complete amplitude of both movements. Patients were thoroughly pre-trained before the first measurement was done.

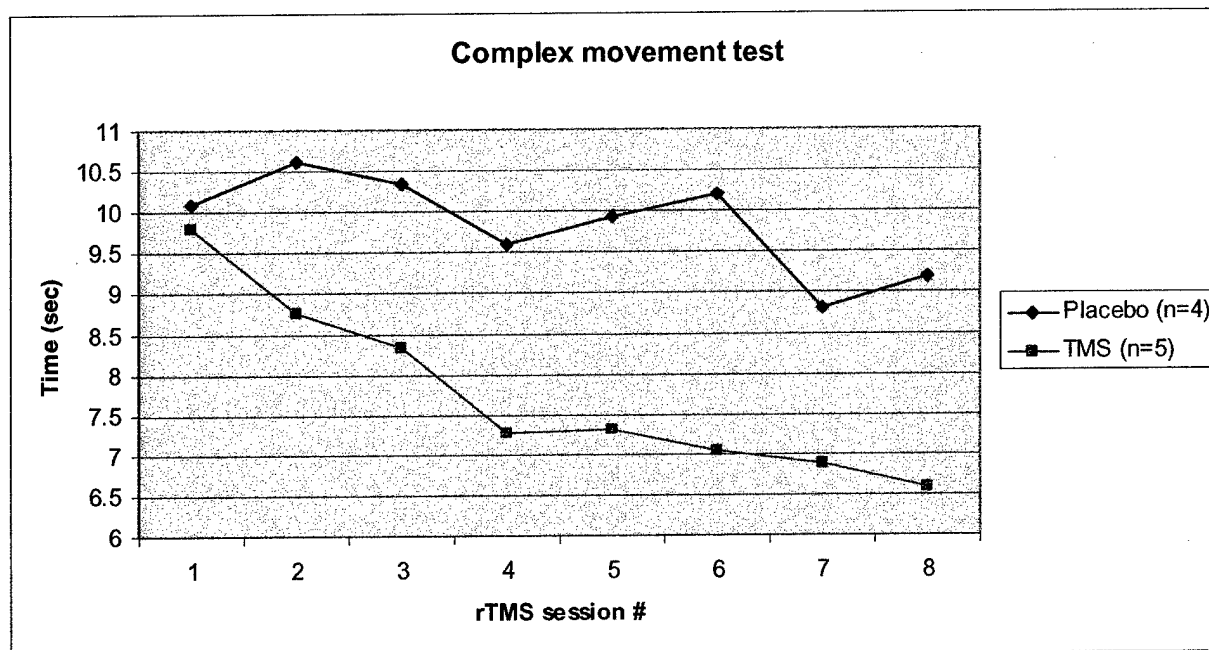


Fig.2. Time of the complex movement test (averaged data).

Abscissa – number of the rTMS sessions done in each of the patients. Ordinate – time of execution of the complex movement test. The measurements for the left and right hand, before and after each rTMS session, are combined. Each point represents four (4) measurements.

Gradual cumulative decrease was observed in patients when the real rTMS was applied. Still, some minor slope existed in the placebo group. Further statistical analysis is needed to prove the difference in the decrease of test execution time over the period of rTMS sessions. If a statistical difference is shown, then the decrease in bradykinesia will be documented by the results of these two tests.

All deviations from the initial investigational plan were reported to the FDA, NINDS IRB, and US Army Research and Materiel Command as amendments before their implementation. These changes in the plan facilitated the process of the recruitment of the patients into the study and were done because of the shortage of patients available. They included the reduction of the minimal L-DOPA dose to 375 mg/day, increase in the minimal time of the 10-meter walking test, payments to patients, advertising in local newspapers, and giving the patients options to be admitted to the Clinical Center for the period of the study. Also, initial and final testing were slightly extended to include the “off” medication period, in comparison to only during the “on” period testing initially.

Key Research Accomplishments

Collection of the data defining clinical effects of the rTMS in patients with PD is in progress. The patient database was developed as a unique part of this study. It includes all experimental data and adverse effects. The purpose of the database is to aid in the storage and analysis of the data.

Reportable Outcomes

The reduction of bradykinesia, which manifested itself in the cumulative decrease of the walk test and complex movement test, will be a reportable outcome after the needed amount of data is collected to show statistical significance of this behavioral effect.

Conclusions

We haven't done any type of the interim statistical analysis of the results and will not do so until enough data has been collected. Preliminary results indicate the cumulative reduction of bradykinesia in the course of rTMS sessions. rTMS used within the parameters of the regimen is safe in patients with PD.

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